(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 September 2001 (13.09.2001)

PCT

(10) International Publication Number
WO 01/66162 A1

(51) International Patent Classification[7]: A61L 27/24, 27/44, 27/50, 15/32

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(21) International Application Number: PCT/EP00/02055

(22) International Filing Date: 9 March 2000 (09.03.2000)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/66162 A1

(54) Title: MULTILAYER COLLAGEN MATRIX FOR TISSUE RECONSTRUCTION

(57) Abstract: A multilayer material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and/or for in ex vivo and/or in vivo reconstruction of tissue or organs according to the invention comprises at least one layer of a natural polymer, preferentially collagen of animal or/and human or/and recombinant or/and transgenic origin, and optionally one or more layers comprising a biocompatible synthetic polymer which may be or not biodegradable, and is obtainable by subjecting the combined layers to a defined heat and defined pressure treatment. The materials of the layers may optionally also contain biologically active substances or substances which improve mechanical, functional, biological and/or handling properties of the material.

MULTILAYER COLLAGEN MATRIX FOR TISSUE RECONSTRUCTION

Description

The invention relates to a novel multilayer material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and/or for in ex-vivo and/or in in vivo reconstruction of tissue or organs, as well as to a process for the manufacture of such novel material.

The use of various different xenogenous, allogenic or autologous collagen-based materials in human and veterinary medicine is known. Such collagen materials can be used for example as hemostatic agent, as a substitute of missing tissue, as a skin equivalent, as a material for tissue augmentation or as a carrier for biologically active substances.

Purified collagen, even of xenogenous origin, is almost fully biocompatible with human (and also animal of different species) collagenous tissue and may be incorporated into and/or subsequently remodeled to a host connective tissue without foreign body reaction and immunologic rejection.

If used as a hemostatic agent, collagen-based material must have both biological and mechanical features promoting hemostasis such as intact collagen fibers and optimal porosity.

For use as tissue substitute (equivalent) the collagen-based material must have optimal matrix properties promoting cell growth, formation of granulation tissue, angiogenesis and vascularization.

As carrier of biologically active substances the collagen-based material must have features allowing an optimal release and pharmacokinetic of incorporated substances.

In all cases, however, the handling of the collagen-based material, its mechanical stability, flexibility and, if necessary, its ability to be sutured or sealed are still most important.

The most popular commercially available collagen-based materials are sponges, membranes or injectable solutions of different viscosity.

For tissue substitution, hemostasis, skin substitution and as a carrier for biologically active substances both collagen-based sponges and membranes have been used in both experimental and clinical studies.

However, there are only few collagen-based drug carriers available on the international market. For example, the only one commercially available collagen-based drug delivery system (for antibiotics) is Collatamp®-G (manufacturer: SYNTACOLL AG, Herisau, Switzerland), also known under 18 different trade names and distributed worldwide by Schering-Plough (USA) and its subsidiaries.

All currently available collagen-based materials are, however, not stable enough to be sutured, rolled, or sticked, especially in areas of mechanical tension or in difficult anatomical sites.

Moreover, collagen sponges or membranes are – in many cases – not strong enough to sufficiently cover defects of such tissue as, i.e., dura mater, superficial and deep skin wounds, bones, nerves, etc.,

To improve the mechanical properties of collagen materials, various additional crosslinking procedures have been described. The most popular are: chemical crosslinking (i.e. with aldehydes) or physical crosslinking (i.e. dehydro-thermal treatment).

The aldehyde-based crosslinking may negatively influence the biocompatibility of collagen and lead to some residues of aldehydes (or its derivatives) in the final product.
The dehydro-thermal treatment, which is used mostly for collagen sponges, has its natural limitation and does not lead to products with the desired properties.

US-Patent 4,655,980 describes the possible manufacturing of a collagen membrane based on a soluble collagen gel suspension. The membrane may be obtained by applying pressure to the gel, or by disrupting the gel and separating the resulting precipitate for casting. Depending on the dimension and shape of the casting mold, either a membrane or solid can be obtained. In fact, the manufacturing of such membrane is based on a commercially available soluble, injectable, atelocollagen product of Collagen Aesthetics, Palo Alto, CA, USA.

The US-Patent 5,219,576 describes a collagen implant material useful as wound healing matrices and delivery system for bioactive agents. Besides manufacturing traditional collagen sponges based on casting and drying of a soluble collagen gel suspension, the patent describes the manufacturing of multilayer material by casting and freezing the individual layers and then lyophilizing the entire composite at once. A possibility of additional crosslinking by both aldehyde and dehydro-thermal processing of the final product is also discussed.

The US-Patent 4,522,753 describes, inter alia, a method for preserving porosity and improving stability of collagen sponges by both aldehyde and dehydro-thermal treatment. The negative pressure (vacuum) used may vary from about 1 mtorr up to slight vacuum just below atmospheric pressure.

The US-Patent 4,578,067 describes a hemostatic-adhesive collagen dressing in form of dry-laid, non-woven, self-supporting webs of collagen

fibers. The manufacturing of such material is based on a Rando-feeder and Rando-webber techniques. The collagen fibers from the Rando-feeder are introduced into the air stream of the Rando-webber and form a fiber mass of uniform density. Such mass may then be processed by pressing or embossing or by calendering at a temperature ranging from room temperature to 95°C.

The US-Patent 5,206,028 describes a collagen membrane having improved physical and biological properties. Such membrane does not swell appreciably upon being wetted and maintains its density. The manufacturing of such translucent, collagen Type-I based material is based on compression of collagen sponges in a roller press with a calibrate aperture followed by aldehyde cross-linking. For additional mechanical stabilization, the cross-linked membrane may be re-wetted, re-lyophilized and pressed again under standard condition.

The US-Patent 4,948,540 describes a mechanically stable, comfortable collagen wound dressing sheet material fabricated by lyophilizing a collagen composition (soluble and insoluble collagen parts in range of 1:20 to 10:1) and compressing the porous pad at a pressure between about 15,000 and 30,000 p.s.i. The material may be also cross-linking by dehydro-thermal treatment to improve mechanical stability.

At present, all of the methods for manufacturing of collagen-based material with improved mechanical, physical and biological properties (as described above) are not in use for industrial manufacturing of such collagen-based material.

There is a need, in both human and veterinary medicine, to create collagen-based materials (or materials based on other natural polymers) with enhanced mechanical and physical properties without increasing

immunologic disadvantages as well as without potential risk for foreign body reaction or granuloma formation.

Moreover, there is a need to create collagen-based constructs in which collagen components can be joined on physical and/or mechanical basis without additional cross-linking substances of potential negative value for living cells or tissue.

Additionally, there is a need to create such collagen-based constructs which can serve for long time tissue substitution (slow degradation or/and incorporation rate) and have high mechanical strength.

There is also a need to create such collagen-based materials which are multilayered and in which each layer can have different mechanical or physical and physiologic properties, incl. wetting time, absorption time and/or remodeling/degradation time.

This is of particular interest, if the construct is meant to be used as a matrix for organ substitution or as a delivery system for biologically active substances or drugs.

It was, therefore, an object of the present invention, to provide collagen-based materials which satisfy the above needs and avoid the drawbacks of the state of the art materials.

This object is solved according to the invention by a multilayer material with improved mechanical, physical, funtional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and/or for in ex vivo and/or in vivo reconstruction of tissue organs wherein the material

comprises layers of

a) at least one material comprising a natural polymer, preferentially collagen of animal or/and human or/and recombinant or/and transgenic (incl similar or adequate techniques) origin

and/or

b) at least one material comprising a an optionally biocompatible and/or biodegradable synthetic polymer,
and wherein the material is obtainable by joining the layers by simultaneous treatment with defined heat and defined pressure.

Within the context of this invention, natural polymer is meant to encompass natural substances which exhibit similar properties as collagen and are useful for the same applications. Examples of such substances are collagen, gelatine and hyaluronic acid. According to the invention collagen is the preferred natural polymer.

This invention allows to permanently or temporarily join different natural polymer- and, preferably, collagen-containing products or layers under formation of a multilayered product
by simultaneously applying defined mechanical pressure and defined heat - to at least two preferably different product layers - in a way which protects the fibrilar - native and/or renaturate - structure of the collagen from degradation or/and denaturation or/and melting and which save the natural biologic properties of collagen (i.e. hemostatic properties or matrix properties).
Moreover, the method used allows to create natural polymer- and, preferably, collagen-based material with improved and variable, but defined, mechanical stability, dry and wet tension, fluid absorption and flexibility.

The present invention allows the joining of at least two layers of the same or different materials. Such layers can either all be natural polymer and, preferably, collagen based or comprise a combination of at least one natural polymer and, preferably, collagen layer with one or more synthetic polymer layer, preferably silicone. The final product –especially in the case of two collagen-based layers in the material - has excellent mechanical properties, especially dry and wet tension. Moreover such material has natural

hemostatic properties, improved wetting abilities, and can be rolled or screwed in dry or wet condition without loosing shape, braking down, etc.

The present invention allows for example the combination (joining) of different collagen fashions such freeze-dried sponges, air-dried membranes, freeze-dried pre-pressed sponges, etc,.

The present invention allows to create novel collagen-based materials such, i.e., leather-like collagen sheets of different strength , collagen "pockets" or "tortellini-like" constructs, collagen "sandwich"-like structures of different permeability and porosity as well as collagen tubes and channels with or without lumen. In the latter case, the "lumen" of the tube (channel) may be filled with other collagen-based material (core) of various density and/or porosity.

The collagen used for manufacture of the improved collagen-based multilayer material of the invention may be either of animal origin (xenogenous to humans) or human origin (autologous or allogenic) or may be obtained from genetically manipulated organisms (recombinant techniques and/or transgenic organisms), or by any other similar or/and equivalent method.

Moreover, due to variations in the manufacturing process, the permeability for air (or other gases) and water (or other fluids, incl. blood, tissue fluids or similar) as well as the mechanical strength of the final product can easily be controlled. The respective methods are basically known to the skilled artisan.

The collagen used for manufacturing of the improved collagen-based material may be of Typ-I, Type-II, Type-III, Type-IV, Type-VII, Type-IX alone or may be a mixture of two or more of such collagens.

As the most important collagen in the human and animal body is the Typ-I collagen, the raw material preferentially used for manufacture of such improved collagen-based multilayer product is the Type-I collagen. This material can be easily obtained i.e. from animal tissue (skin, tendons, etc.,) by industrial methods according to state-of-the-art, GMP-conformed techniques.

Both enzymatically treated or not enzymatically treated collagen can be used for manufacture. If treated with proteolytic enzymes, non-helical parts of the collagen molecule will be separated from the triple-helical collagen chain (atelocollagen).

To obtain the novel multilayer membrane-like material of appropriate mechanical and physiological properties, different layers a natural polymer, preferentially pre-pressed collagen membranes, non-pre-pressed collagen sponges or air-dried collagen membranes alone or in different combinations may be used.

Alternatively, the novel multilayer membrane-like material may contain at least one artificial (synthetic) polymer membrane which may be or may be not biodegradable together with at least one layer of a natural polymer material.

To join different basic products to yield the novel multilayer material, a simultaneous treatment with controlled heat and controlled pressure is applied.

The use of defined mechanical pressure for industrial manufacture of collagen membrane-like products based on freeze-dried collagen sponges containing active substances, i.e. antibiotics like gentamycin, is known per se (i.e. EP 0 069 260, issued 09/25/1985, owned by Syntacoll AG, Herisau, Switzerland).

The influence of a moderate heat, especially if used together with a negative pressure (vacuum), for induction of additional cross-linking sites

in collagen sponges has been described previously as dehydro-thermal treatment (see above).

The present invention now combines heat and positive pressure (mechanical pressure), both known per se to the skilled worker, for the treatment of the basic materials according to the present invention. Such combination has never been proposed before, but leads to products with highly unexpected, superior properties, as described above.

The temperature used lies preferably in a range of from 50°C to 200°C. The pressure used lies preferably in a range of from 0.1 to 1000 kg/cm^2. The time period of the thermal pressing procedure lies preferably between 0.1 second to 1 hour.
The treatment can be conducted in a conventional thermal pressing machine in which the parts exerting the pressure can be adjusted to a predefined and constant temperature. The manufacturing steps used for the preparation of the novel multilayer material can be easily incorporated into routine manufacturing process and allow to save time and costs if compared to other currently used methods used for the production of collagen membranes etc.

As a result of such a heat and pressure treatment, a collagen-containing membrane-like structure of desired thickness, mechanical strength, permeability, degradation and resorption time, etc., can be manufactured.

Moreover, the manufactured product is much better in handling than other known collagen based products such as freeze-dried sponges or air-dried membranes.

The basis material for manufacturing the novel multilayer material is preferably a pre-pressed, non-transparent collagen membrane, non pre-

pressed collagen sponge, a transparent collagen membrane or a combination of these products.

The collagen sponge may be manufactured using various state-of-the-art techniques. The basis for such a material may be collagen dispersion / suspension (i.e. in water or other non-organic solvent) of 0.5 to 5.0 weight% of dry collagen.
The sponge can obtained preferably by freeze-drying.

To improve basic mechanical properties, the collagen sponge itself can preferably be treated simultaneously with defined heat and defined pressure, to obtain a non-transparent, membrane-like structure.
The temperature used for such treatment again preferably lies within a range of from 50°C to 200°C.
The pressure used for such treatment also again lies in a range of from 0.1 to 1000 kg/cm^2.
The time period for the thermal pressing procedure is preferably set between 0.1 seconds and 1 hour.

A transparent collagen membrane may be manufactured using different state-of-the-art techniques. The basis for such a material may also be collagen dispersion / suspension (i.e. in water or other non-organic solvent) of 0.5 to 5.0 weight% of dry collagen.
The membrane will preferably be obtained by controlled air-drying.
Such preformed membranes, preferably, can be used as one or more of the layers on collagen basis.

The material used for manufacturing such multilayer material according to the invention may be a natural polymer or/and artificial (synthetic) polymer in various different structure. This allows for the combination of either only natural polymers of the same or different kind, as well as the combination of (optionally several) natural polymers and synthetic polymers to form a

multilayer structure of the invention and useful for the above mentioned applications and indications.

Both the natural polymer material and the synthetic polymer material optionally may contain further substances like biologically active substances such as hemostatic agents, growth factors, cytokines, hormones, drugs (i.e. antibiotics, antiinflammatory agents or the like), etc. or biologically important and tissue-compatible inorganic or/and organic substances or/and their derivatives which can improve the mechanical, functional, biological and handling properties of the material.

Another subject of the present invention is the process for the manufacture of the multilayer material of the invention, as already described above in detail as to basic materials used and process conditions.

Still another subject of the present invention is the use of the novel multilayer material of the invention for the indications and applications mentioned above in the context of the description of the material.

The invention will be further described and illustrated by the following examples.

EXAMPLES

Note: using different amounts of basic collagen sponges or basic collagen membranes both mechanical properties and biological function (especially remodeling/degradation ratio) of the final material can be influenced. Moreover, using different forms of basic material (non-preprocessed or pre-processed) as well as various different ingredients (i.e. biologically active substances) incorporated into the basic material, the degradation ratio and release ratio may be influenced (controlled) in various different ways.

In these examples the manufacturing of the simplest material made from two or three similar or different basic materials (sponges or/and membranes) will be described.

Example 1

Manufacture of a novel multilayer collagen-based membrane-like material from two (or more) basic, not pre-pressed sponges.

Two freeze-dried collagen sponges (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be conditioned at 21°C in a moisture chamber to a water content of 14%. After conditioning, the sponges are placed one above the other to form a double-layer and prepared for thermo-mechanical pressing.

The continuous heat and pressure, 100°C and 25 kg/cm^2 respectively, is applied to the sponges for 10 seconds to form a double-layer construct.

After pressing, the surfaces of the press are opened without pre-cooling.

The collagen-based double-layer membrane obtained is not transparent. It has an excellent mechanical stability, flexibility, good fluid absorption and good hemostatic properties.

The collagen layers are joined physically, the mechanical stability of the junction is very high.

The material obtained can be used in various medical applicationd in both ex vivo and in vivo situation.

Example 2

Manufacture of a novel multilayer collagen-based membrane-like material (pre-pressed sponges)

Two freeze-dried collagen sponges (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be pressed to a double-layer membrane as in Example 1. After pressing, the membranes are conditioned to a water content of 10-15% and placed one above the other to form a double-layer and prepared for thermo-mechanical pressing.

The continuous heat and pressure, 100°C and 25 kg/cm^2 respectively, is applied to the sponges for 10 seconds to form a new double-layer construct. Each layer of this material consists of two previously pressed sponges of defined porosity.

After finishing pressing, the surfaces of the press are opened without pre-cooling. The collagen-based double-layer membrane obtained is not transparent. It has an excellent mechanical stability, flexibility, good hemostatic properties, but only limited fluid absorption due to the very low porosity.

The collagen layers are joined physically, the mechanical stability of the junction is very high.

The material obtained can be used in various medical applications in both ex vivo and in vivo situation.

Example 3

Manufacture of a novel multilayer collagen-based membrane-like material (not pre-pressed sponges + pre-pressed sponges)

Two freeze-dried collagen sponges (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be conditioned at 21°C in a moisture chamber to a water content of 14%. After conditioning, the sponges are placed one above the other to form a double-layer and prepared for thermo-mechanical pressing. This will lead to a double-layer construct as in Example 1.

On the top of this material, an additional freeze-dried collagen sponge (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be placed. In such case, two layers of this material consist of two previously pressed sponges, the third one of a not-pressed sponge of defined porosity. This three-layer construct is then pressed to a membrane. A continuous heat and pressure, 100°C and 25 kg/cm^2, respectively, is applied to the sponges for 10 seconds to form a new three-layer construct.

After finishing pressing, the pressure surfaces are opened without pre-cooling. The collagen-based double-layer membrane obtained is not transparent. It has an excellent mechanical stability, flexibility and good hemostatic properties. The previously pre-pressed layer has a very limited fluid absorption, but the third (spongy) layer has an excellent fluid absorption and can absorb a fluid amount of up to 10 times of the own weight.

All collagen layers are joined physically, the mechanical stability of the junction is very high.

The material obtained can be used in various medical applications in both ex vivo and in vivo situation, especially as a wound covering material, hemostatic material, etc.

Example 4

Manufacture of a novel multilayer collagen-based membrane-like material (not pre-pressed sponges + air-dried membrane)

A freeze-dried collagen sponge (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) is conditioned at 21°C in a moisture chamber to a water content of 14%.

On the top of this sponge, an air-dried transparent collagen membrane (i.e. Collatamp-Fascia®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be placed. The Fascia is conditioned to a water content of 20%. This

double-layer construct is then pressed to a membrane. A continuous heat and pressure, 100°C and 25 kg/cm², respectively, is applied to the sponges for 10 seconds to form a new double-layer construct.

After finishing pressing, the surfaces or the press are opened without pre-cooling. The collagen-based double-membrane obtained is not transparent. It has an excellent mechanical stability, flexibility and good hemostatic properties. The previously spongy layer has an excellent fluid absorption and can absorb a fluid amount of up to 10 times of the own weight. The previously fascia layer remains hemostatic, but absorbs fluids in only limited quantity. This layer serves both as mechanical and biological barrier of limited water and air permeability covering the surface of the product. Both collagen parts are joined physically, the mechanical stability of the junction is very high.

The material obtained here can be used in various medical applications in both ex vivo and in vivo situation, especially as a wound covering material, hemostatic material, dressing for split- of full-skin donor sites, etc.

Example 5

Manufacture of a novel multilayer collagen-based membrane-like material (pre-pressed sponges + air-dried membrane)

Two freeze-dried collagen sponges (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be conditioned at 21°C in a moisture camber to a water content of 14%. After conditioning, the sponges are placed one above the other to form a double-layer and prepared for thermo-mechanical pressing. This will lead to a double-layer construct as in Example 1.

On the top of this material, an air-dried transparent collagen membrane (i.e. Collatamp-Fascia®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be placed. The Fascia is conditioned to a water content of 20%. In

such case, two layers of this material consist of two previously pressed sponges, the third one of a not-pressed but flexible collagen mambrane. This three-layer construct is then pressed to a membrane. A continuous heat and pressure, 100°C and 25 kg/cm^2, respectively, is applied to the sponges for 10 seconds to form a new three-layer construct.

After finishing pressing, the press surfaces are opened without pre-cooling. The collagen-based triple-layer membrane obtained is not transparent. It has an excellent mechanical stability, flexibility and good hemostatic properties. The previously spongy layer has lower fluid absorption than previously not pre-pressed one, and can absorb a fluid amount of up to 10 times of the own weight. The previously fascia layer remains hemostatic, but absorbs fluids in only limited quantity. This layer serves both as mechanical and biological barrier of limited water and air permeability covering the surface of the product.

Both collagen parts are joined physically, the mechanical stability of the junction is very high.

The material obtained here can be used in various medical applications in both ex vivo and in vivo situation, especially as a wound covering material, hemostatic material, dressing for split- of full-skin donor sites, etc.

Example 6

Manufacture of a novel multilayer collagen-based material in form of tubes of channels with open lumen.

Two freeze-dried collagen sponges (i.e. Collatamp®, manufacturer: SYNTACOLL AG, Herisau, Switzerland) will be conditioned at 21°C in a moisture chamber to a water content of 14%. After conditioning, the sponges are placed one above the other to form a double-layer and prepared for thermo-mechanical pressing. This will lead to a double-layer construct as in Example 1.

This construct will be then turned around a tube made from not adhesive, thermo-stable agent (i.e. medical grade paper) and thermally pressed to obtain a collagen-membrane tube. A continuous heat and pressure, 100°C and 25 kg/cm^2, respectively, is applied to a period of sponges for 10 seconds. After finishing pressing, the press' surfaces are opened without pre-cooling. The collagen-based tube obtained is not transparent. It has an excellent mechanical stability, flexibility and good hemostatic properties. The central part – non adhesive material can be easily removed directly after manufacturing or later, i.e., directly before use.

After wetting, the tubular construct has an excellent mechanical stability and flexibility. It can be used for guiding tissue reconstruction, i.e. for reconstruction of tubular organs or nerves.

Example 7

Manufacture of a novel multilayer collagen-based material in form of tubes or channels in which the lumen is filled by the core made of an other collagen material of different porosity.

The product is made from freeze-dried and pre-pressed collagen membrane(s) and from a freeze-dried non-pre-pressed collagen sponge of different porosity in a similar way as described in Example 6. The not pre-pressed sponge is covered from all sides by pre-pressed collagen membrane(s) and treated simultaneously with heat and pressure to form a multilayer construct. A continuous heat and pressure, 100°C and 25 kg/cm^2, respectively, is applied to a period of sponges for 10 seconds. After finishing pressing, the press surfaces are opened without pre-cooling. The collagen-based tube obtained is not transparent. It has an excellent mechanical stability, flexibility and good hemostatic properties. The final material creates a construct with a core of different porosity. The core will absorb fluids up to 20x its own weight. The core is protected by a low-

swelling collagen membrane. This construct can be used i.e. for reconstruction of missing tissue incl. bones and nerves.

Example 8

Manufacture of a novel multilayer collagen-based membrane-like material in form of tubes or channels in which the lumen is filled by a core of an other collagen material of different porosity and in with core has additional longitudinally oriented channels.

The final product is manufactured as in Example 7, but additional longitudinally oriented channels are created in the core of the tube by incorporation of wire(s) of various diameters into the core material prior to manufacturing such tubes (see Example 7).

Claims

1. A multilayer material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and/or for in ex-vivo and/or in vivo reconstruction of tissue or organs, containing at least one layer of a natural polymer, preferentially collagen, of animal, or/and human or/and recombinant or/and transgenic (incl. similar or adequate techniques) origin
and optionally one or more layers of a biocompatible synthetic polymer which may be or may be not biodegradable,
wherein the material is obtainable by subjecting the combined layers to a defined heat and defined pressure treatment.

2. A multilayer material according to claim 1, wherein one layer used for manufacturing is a sponge or a membrane containing 0.5 – 5 weight% of collagen.

3. A multilayer material according to claim 1 or 2, wherein collagen layers have been previously simultaneously treated with defined various heat and pressure.

4. A multilayer material according to anyone of claims 1 to 3, wherein the temperature used for the heat treatment lies within 50°C and 200°C.

5. A multilayer material according to anyone of claims 1 to 4, wherein the pressure used lies within a range of from 0.1 to 1000 kg/cm^2.

6. A multilayer material according to anyone of claims 1 to 5, wherein the time period of the thermal pressing procedure lies within 0.1 second and 1 hour.

7. A multilayer material as in anyone of claims 1 to 6, wherein at least one natural polymer is a collagen in form of non-pressed sponges, pre-pressed sponges, air-dried membranes or all of these in various different combinations.

8. A multilayer material material according to anyone of the preceding claims, wherein one or all of the components have or have not been crosslinked (chemically, physically or using other known crosslinking techniques) prior to manufacturing the final multilayer product.

9. A multilayer material according anyone of the preceding claims, wherein the final product is a tube or channel with or without lumen.

10. A multilayer material according to anyone of the preceding claims, wherein the final product is a tube with a core of various different porosity and if the core has or has not additional longitudinally and/or transversally oriented channels.

11. A multilayer material according to anyone of the preceding claims, wherein the layers of natural and/or synthetic polymer material further comprise biologically active substances , such as hemostatic agents, growth factors, cytokines, hormones, drugs (like antibiotics, anti-inflammatory agents) etc. and/or biologically important and tissue-compatible inorganic or/and organic substances or/and their derivatives which can improve at least one of the mechanical, functional, biological and handling properties of the material.

12. Process for the manufacture of a multilayer material of anyone of claims 1 to 11, comprising subjecting at least two layers of material, wherein at least one layer comprises a natural polymer, preferentially collagen of animal or/and human or/and recombinant or/and transgenic (incl. similar or adequate techniques) origin, and optionally one or more layer comprise at least one biocompatible synthetic polymer which may be or may be not biodegradable, to a defined heat and defined pressure treatment.

13. Use of the multilayer material according to anyone of claims 1 to 11 in human and veterinary medicine in both in vivo and in vitro condition and/or for in ex vivo and/or in vivo reconstruction of tissue or organs.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/EP 00/02055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/24 A61L27/44 A61L27/50 A61L15/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 948 540 A (NIGAM ALOK) 14 August 1990 (1990-08-14) cited in the application abstract column 4 ---	1-8, 11-13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2 November 2000	09/11/2000

Name and mailing address of the ISA	Authorized officer
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